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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,345	01/14/2004	Sudhir Agrawal	HYB-018US1	3490

7590 09/17/2008

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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/757,345	AGRAWAL ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 August 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1 and 31*.
   Claim(s) withdrawn from consideration: *3,5,10-16,18,32,40,42,95,99 and 147*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Joseph T. Woitach/
Supervisory Patent Examiner, Art Unit 1633

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1 and 31 stand rejected for reasons of record in the Office Action mailed June 23, 2008. Applicant requests reconsideration after Final Office Action.

Response to Arguments regarding the rejection under 35 U.S. C. 103
Applicant argues that:
a) the cited art does not teach or suggest an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker. Furthermore, Applicants disagree with the Office Action's characterization of the cited art and the alleged motivation to combine the cited art to reach the instantly claimed compound.

b) Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed little or no immunostimulatory activity (see page 809, column 2, lines 22-24). Therefore, not only is the use of the instantly claimed RpG dinucleotide not obvious in view of the prior art, the fact that the instantly claimed compound generated an immune response is a surprising result.

c) the compounds of Kandimalla ('757) are structurally different compounds from the instantly claimed compounds, e.g. two oligonucleotides linked at their 3' ends or internucleoside linkages or a functionalized nucleobase or sugar to a non-nucleotidic linker. Kandimalla ('757) also describes the direct 3'-3', 5'-3', 3'-5' and 5'-5' linkages of two oligonucleotides (see Figures 5-10 and Figure 17).

d) The Office Action continues to wrongly examine the claimed compounds as an "oligonucleotides" in the traditional sense of the term, e.g. mRNA. The claimed compounds do not interact with its target through the well understood mechanism of Watson-Crick base-pairing. Rather, these compounds are ligands for a Toll like receptor (e.g., TLR9), acting through mechanisms which are not well understood, and are novel chemical entities comprising multiple "R" groups. In the absence of a well-understood mechanism, the effect of altering a particular R group in a key portion of the molecule cannot be predicted. Thus, the claimed compound cannot be treated like "oligonucleotides" as previously understood, but rather as novel chemical entities. Simmonds use of base analogs that can still form base pairs through Watson-Crick base pairing is meaningless in the field of the instant application. Simmonds provides no teaching or suggestion regarding the effect that the describe base analogs would have on the immunostimulatory properties of a CG-containing oligonucleotide, much less the effect these bases would have if incorporated into the CG dinucleotide.

e) Although Kandimalla ('757) describes the positional modifications of CG-containing oligonucleotides and that many of these compounds elicit a general enhanced or reduced immune response; it is only the enhanced or reduced immune response that is reproducible based on the position modification. However, at the level of each specific immunomer, the different modifications and combinations thereof result in compounds that, although many of which are immunostimulatory and elicit many of the same cytokines, they each elicit the particular cytokines to different degrees, thereby creating a unique immune response profile. This is important because even a slight of degree change in the elicitation of one or more cytokines can have significant physiological effects.

Applicant's arguments have been fully considered but are unpersuasive.
With respect to a-c), it is unclear how the teachings of Kandimalla (2001), Kandimalla (2002) and Simmonds (1999) fail to teach or suggest the instantly claimed genus of oligonucleotide(s). Kandimalla (2001) taught the ability to synthesize oligonucleotides comprising variations of the CpG motif, YpG and CpR, respectively, in which the "Y" moiety represents a monocyclic or bicyclic cytosine analog and the "R" moiety represents a bicyclic guanine analog, including 2' deoxyguanosine, 2'- deoxy-7-deazaguanosine, and other non-natural purine nucleosides. Thus, those of ordinary skill in the art routinely practiced substitutions of the C and G moieties of a CpG motif to generate YpG and/or CpR motifs prior to the invention. Kandimalla et al (2002) disclose immunomer compounds comprising at least two oligonucleotides linked at their 3' ends, e.g. 3'-3' as annotated in the rejection and acknowledged by Applicant, as well as via non-nucleotidic linkers or internucleoside linkages, wherein said immunomers comprised C*pG* immunostimulatory motifs wherein the instantly claimed G* moieties are disclosed. Simmonds teaches base analogs having the structure illustrated in Figure 24 of the instant specification. The deoxy-P-base nucleoside oligos of Kandimalla (2001) were not tested in the context of being linked at their 3' ends or internucleoside linkages or a functionalized nucleobase or sugar to a non-nucleotidic linker, as per the instant claims. Thus, conclusions drawn from this reference alone is not commensurate in scope to the claimed invention. Furthermore, the claims do not place a required amount of immunostimulatory activity achieved by the claimed genus of immunomers. The "little immunostimulatory activity" reasonably fulfills the functional requirement. Thus, it is unclear how the ability of the instantly claimed genus of compounds, i.e. an oligonucleotide comprising a P-base (Kandimalla, 2001) having the structure illustrated in Figure 24 of the instant application (Simmonds) in the context of at least two oligonucleotides linked at their 3' ends (Kandimalla, 2002) to generate an immune response is a surprising result in light of the genus of compounds disclosed in the prior art and the teachings demonstrating the routine substitution of C* and G* isostructures.

With respect to d), the combination of the Kandimalla and Simmonds references teach that both the bicyclic P-base analogs and the instantly claimed bicyclic cytosine analog share the oxygen and nitrogen hydrogen bond acceptor and nitrogen bond donor atoms on the same face so as to establish hydrogen bonding with another surface in the same manner as cytosine. Thus, such cytosine analogs are recognized in the art as being isostructural with natural cytosine. While the mechanism of receptor-ligand interaction may not be well understood, as per Applicant's argument, Applicant has presented no evidence that the claimed compounds do not molecularly interact with its target through hydrogen bonds. Rather, the Examiner notes that Applicant's own work teaches that several other purine and pyrimidine modifications with required hydrogen bond acceptor and donor groups at appropriate positions are under study for their immunostimulatory activity in place of natural guanine and cytosine in the CpG motif (Kandimalla et al, 2001; pg 812, col. 1, ¶3).

With respect to e), "Products of identical chemical composition can not have mutual exclusive properties." Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its

properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. In re Spada, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. In the instant case, the genus of claimed immunomers are merely required to have immunostimulatory activity, which is an inherent property. The claims do not require the genus of compounds to elicit a specific cytokine(s) to a specific amount(s) of expression so as to achieve a specific physiological effect(s).

Response to Arguments regarding the Double Patenting rejections
Applicant argues that:
a) with respect to 10/694383, 10/694586 and 7,276,489, a YpG-containing oligonucleotide in which Y is a deoxy-P-base nucleoside showed little or no immunostimulatory activity. Thus, the instantly claimed RpG dinucleotide is not obvious in view of the prior art because the instantly claimed compound surprisingly generated an immune response.

b) the other applications are later-filed applications, and thus Applicants will consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed application.

Applicant's arguments have been fully considered but are unpersuasive.
With respect to a), the claims do not place a required amount of immunostimulatory activity achieved by the claimed genus of immunomers. Thus, "little immunostimulatory activity" reasonably fulfills the functional requirement.

With respect to b), the provisional ODP rejections will be maintained until the aforementioned issues are resolved.